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Exploration of Emulgels as a Promising Carrier for Natural Oils in the Treatment of Onychomycosis

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ABSTRACT:
Onychomycosis is a common fungal infection of the nails that can be painfully, disfiguring and severely impact quality of life. Systemic and topical antifungal agents have limited efficacy, adverse effects and may fuel antimicrobial resistance. Potential treatment of fungal nail infections with natural oils: tea tree oil, garlic oil, and oleic acid are explored in this review. Unlike other oils, these oils do have antimicrobial properties but it needs better delivery system for enhanced bioavailability and stability. The solution to this challenge lies in emulgels that combine nanoemulsions and lipid nanoparticles to provide sustained release, targeted delivery and improved therapeutic outcomes. In this article, the emulgels of natural oils formulation, its action mechanism for the antifungal, is discussed along with their advantages in overcoming the limitations of the conventional treatment is discussed. The emulgels are also reviewed with regards up to their synergistic effects, the safety profile and the challenges in large scale production and approval as these processes. The therapeutic potential of emulgels in treating onychomycosis is demonstrated and their use leads to further research and clinical application.

KEY WORDS: Onychomycosis, emulgels, natural oils, antifungal properties, garlic oil, nanoemulsions, bioavailability, sustained release

I. INTRODUCTION

Dermatological care in respect to nail infections, especially when due to fungi, bacteria or yeast are tough things, causing discomfort, suffering and disfigurement [1]. While these treatments are effective, they often are burdened by negative side effects and the creation of resistant microbial strains, calling for the approach of alternatives [2]. Tea tree oil, garlic oil and oleic acid are natural oils that have antimicrobial properties and could therefore be used to address fungal infections. This beneficial combination of oils are then further enhanced by enclosing them in nanoemulsions and lipid nanoparticles to enhance their bioavailability and stability and improve their therapeutic efficacy. By these formulations, slow release of the active ingredient is not only achieved, but also an approach with a targeted delivery of the active ingredients to the site of infection is achieved to maximize treatment outcomes. Natural oils with inherent antimicrobial properties present a promising avenue for delivering topical formulations, but natural oils, particularly other than preservatives, have limited stability when combined with water and are susceptible to oxidation; hence, a way of delivering natural oils head on to the site of infection with extended shelf life and stability would be a desirable formulation that seeks to bridge this gap [3]. Thanks to their capability over the other limitation of gels that is the delivery of hydrophobic drugs [4], emulgels overcome this limitation. Natural oils can be readily incorporated into emulgels thereby improving the therapeutic potential of these emulgels by using their antimicrobial, anti inflammatory, and antioxidant properties [5], and gel matrix gives a sustained release of active ingredients protecting them from degradation, improving their therapeutic effect. The dual nature of emulgels enables their use as a means to create stable formulations that can deliver natural oils to the organic tissue at and surrounding the nail bed. Overall, the use of nail infections can be managed by an integration of emulgels with natural oils.

In this review potential of emulgels in delivery of natural oils for treatment of fungal nail infection is explored with emphasis on formulation, advantages and efficacy.

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II. ONCHOMYCOSIS

A fungal infection of the nails, onychomycosis is found to be highly prevalent in the general population of the world. The most common causes are dermatophytes, yeasts, and non dermatophytes molds resulting in nail discoloration, thickening and brittleness. Onychomycosis resulting from the dermatophytes is called tineaunguium. A dystrophic nail is one that is not abnormal due to fungal infection. Both fingernails and toenails can be infected by onychomycosis, but onychomycosis of the toenail is more common [6].

Onychomycosis is the most frequent fungal foot infection and has been estimated at 27% in a 2003 survey of diseases of the foot in 16 European countries. The prevalence increased with age. In Canada, estimates were 6.48%. One third of diabetics and 56% more frequently in those with psoriasis have onychomycosis [7].

2.1 Classification of Onychomycosis

There are five classic types of onychomycosis:

- **Distal subungualonychomycosis** is the most common form of tineaunguium and is usually caused by Trichophytonrubrum, which invades the nail bed and the underside of the nail plate.
- **White superficial onychomycosis (WSO)** is caused by fungal invasion of the superficial layers of the nail plate to form "white islands" on the plate. It accounts for around 10 percent of onychomycosis cases. In some cases, WSO is a misdiagnosis of "keratins granulations" which are not a fungus, but a reaction to nail polish that can cause the nails to have a chalky white appearance. A laboratory test should be performed to confirm.
- **Proximal subungualonychomycosis** is fungal penetration of the newly formed nail plate through the proximal nail fold. It is the least common form of tineaunguium in healthy people, but is found more commonly when the patient is immunocompromised.
- **Endonyxonychomycosis** is characterized by leukonychia along with a lack of onycholysis or subungual hyperkeratosis.
- **Candidalonychomycosis** is Candida species invasion of the fingernails, usually occurring in persons who frequently immerse their hands in water. This normally requires the prior damage of the nail infection or trauma [8].

2.2 Conventional Treatment of Onychomycosis:

Systemic antifungals have the best effect in the treatment of onychomycosis and are the first step of choice where lesions are present to a moderate degree or in the case of patients with diabetes. Outcomes may be improved by combination therapy with topical agents, debridement or nail avulsion. Oral antifungals such as terbinafine and itraconazole, and topical agents like ciclopirox as well as efinaconazole are standard treatments. Cure rates of 55% for efinaconazole and 36% for either tavaborole or ciclopirox have been demonstrated for topical treatments in mild to moderate cases. Of all the systemic terbinafine groups the mycological cure rates are the highest (76%) and the complete cure rate the highest (of 38%).

Severe cases should be treated by oral therapy, although this may not be possible for certain patients as there are medical contraindications or because of personal preference. Topical therapies have improved that are FDA approved, but have low complete cure rates (as efinaconazole at 18%).

Before systemically treatment, patients should be screened for liver disease and undergo hepatitis tests at five weeks. It should be considered in drug interactions, especially with azole antifungals and statins. The selective access to terbinafine is generally safe but contraindicated with certain psychotropic medications. Alternative therapies or debridement alone may be preferable to adverse effects in high risk patients. Nevertheless, these treatments tend to be limited by long treatment course, high recurrence rates, and potential systemic side effects. This has led to an increase in the search for other and natural remedies and natural oils such as garlic oil which exhibits antifungal activity [9].

III. NATURAL OILS AND THEIR ANTIFUNGAL PROPERTIES

Natural oils have gained profound attention for their antifungal properties and lesser side effects and provide best alternative therapies to conventional treatments for onychomycosis. Research has been carried out on essential oils such as neem oil, eucalyptus oil, clove, tea tree, oregano, rosemary and Zatariamultiflora for efficacy against the fungi that cause onychomycosis. These plant derived oils contain bioactive compounds which inhibit growth of pathogenic fungi and could be used for treatment and management of nail infections and could provide advantages over

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current treatments, such as antimicrobial resistance and the limitations of standard therapies [10, 11].

3.1 Specific Natural Oils and Their Antifungal Efficacy

1. Clove Oil (Syzygiumaromaticum)

Eugenol rich clove oil has been shown to have strong antifungal activity against a number of fungal pathogens. It has been established in studies that clove oil can kill the growth of Penicilliumdigitatum [12], Fusariumoxysporum [12], and Rhodotorulamucilaginos [13]. This is because the effectiveness of this agent derives from its capacity to interfere with the integrity of fungal cell membranes and to interfere with essential enzymes.

2. Thyme oil (Thymus vulgaris)

Most studies have reported about the antifungal activity of thymol, one of the major active compounds in thyme oil. It is effective against Penicilliumdigitatum; Aspergillusflavus, and Candida albicans [15]. According to its antifungal activity, thyme oil is considered to be altering fungal cell membrane permeability and affecting the metabolism of the cells.

3. Cinnamon Oil (Cinnamomumzeylanicum)

Cinnamon oil is considered to contain cinnamaldehyde, which has been proven to be highly effective on Penicilliumdigitatum [16], Fusariumoxysporum [17], and Candida albicans [17]. It carries out its antifungal activity by interfering in the fungal cell wall synthesis and inhibiting fungal cell membrane synthesis.

4. Oregano oil (Origanumvulgare)

Rich component of Oregano oil, Carvacrol has shown powerful effects against Penicilliumdigitatum, Fusariumoxysporum and Candida albicans. The thought is that its antifungal properties involve disrupting fungal cell membrane, and blocking the enzymatic processes key to life in the fungi.

5. Tea Tree Oil (Melaleucaalternifolia)

There is good evidence of considerable antifungal activity of tea tree oil, especially its terpinen-4-ol component, against dermatophytes, such as Trichophytonrubrum. It has been shown that tea tree oil possesses potent activity against both Trichophytonmentagrophytes and Microsporumcanis which are common causes of dermatophytosis [18]. Tea tree oil used in this study has been demonstrated to be efficacious against Penicilliumdigitatum [42], Aspergillusflavus [43], and Candida albicans [43]. This is due to its disruption of the fungal cell membrane integrity and inhibition of essential metabolic pathways. Studies in the laboratory have shown that tea tree oil can be a viable alternative treatment, but the need for further clinical studies to establish if it is long term effective and safe are needed [19].

6. Eucalyptus Oil (Eucalyptus citriodora)

Most of the constituents of Eucalyptus oil are citronellal, but is reported to possess antifungal activity against Penicilliumdigitatum and Fusariumoxysporum. Estimated antifungal activities originate from its capacity to disrupt fungal cell membranes and inhibit distinct enzymatic reactions.

7. Rosemary Oil (Rosmarinusofficinalis)

Rosemary oil, rich in camphor and borneol, has shown antifungal activity against Penicilliumdigitatum and Aspergillusflavus. Its antifungal properties are thought to arise from its ability to disrupt fungal cell membranes and inhibit essential metabolic pathways.

8. Caraway oil (Carumcarvi)

Carvone has been shown to be one of the major components of caraway oil that exhibits antifungal activity against Aspergillusfumigatus [20]. The antifungal properties of the drug are due to the ability of it to block the entry of amino acids, the disruption of the fungus cell membrane function, and its ability to inhibit ergosterol biosynthesis.

9. Lemongrass Oil (Cymbopogoncitratus)

It has been reported that antifungal activity of lemongrass oil against Penicilliumdigitatum and Aspergillusflavus contains citral rich oil. Due to its ability to disrupt fungal cell membranes and inhibit essential enzymatic processes, its antifungal properties are thought to be due to it.

10. Bergamot Oil (Citrus aurantiumbergamia)

Generally containing limonene, bergamot oil has been shown to have antifungal activity against Penicilliumdigitatum and Fusariumoxysporum. It is believed to acquire these antifungal properties by disrupting the fungal cell

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membrane and by inhibition of essential metabolic pathways.

11. Garlic Oil (Allium sativum)

It is known that garlic has shown a very good antimicrobial and antifungal properties. These effects are due to the primary bioactive compound responsible for these effects, allicin, produced when garlic is crushed or chopped. Strong antifungal activity has been demonstrated against a variety of pathogens, Trichophytonrubrum and Candida albicans in particular which are both common causative agents of onochomycosis, for allicin and its derivatives including diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyltrisulfide (DATS) [21].

12. ZatariaMultiflora Oil

Clinically trials have shown significant inhibitory effect of Zatariamultiflora essential oil incorporated to a nanostructured lipid carrier gel on fungal growth. In patients with onychomycosis associated with Candida, this formulation gave better clinical and mycological outcomes [22].

3.2 Synergistic Effects of Essential Oils

This research has also shown that the synergistic effects of these natural oils will increase their antifungal efficacy thus providing better treatments for different fungal infections. These oils are useful not only for topical applications but also in formulations for shampoo and creams, which helps sustain their use in fighting fungal problems further.

Other essential oils and other antifungal agents have been found to synergize with essential oils when they are combined. For example:

1. Thyme and oregano oils and antifungal drugs (nystatin and fluconazole) produced synergistic antifungal action against Candida albicans [23].
2. Anti fungal activity in the combination of clove and cinnamon oil against Penicilliumdigitatum was shown.
3. Synergistic effect of Aspergillusfumigatus with lemongrass and thyme oils has been reported.
4. Clove Oil, Turmeric, and Peppermint: Clove oil, rich in eugenol, exhibits strong antifungal properties. All together, the combination of turmeric's curcumin with its anti-inflammatory and antimicrobial effect and peppermint with its antifungal and soothing qualities, makes this herbal cream a good treatment for onychomycosis when used together [24].
5. Antifungal Nail Lacquer: A nail lacquer containing biogenic silver nanoparticles, oregano and rosemary essential oils, exhibited very promising antifungal results. This formulation makes natural and innovative formulation that provides onychomycosis treatment efficiently permeating nail and damages fungal structures [25].
6. Formulation of emulgels with Fluconazole solid dispensions and their antifungal activity: The study assesses the antifungal activity of the emulgels containing Tea tree oil, Neem oil and Lemon grass oil.

3.3 Mechanisms of Antifungal Action

The increased interest in natural remedies has rendered an important offer to investigate the mechanisms by which these bioactive compounds may antifungal embodiments, which has brought about innovative methods of infection management. Understanding these processes not only improves the existing treatments, but it also facilitates the development of new antifungal agents with less potential to induce resistance in order to maintain the efficacy and sustainability of fungal infection management.

Several mechanisms attributed the antifungal activity of natural oils to include:

1. Alteration of Permeability of Fungal Cell Membranes: The essential oils are able to disrupt fungal cell membranes and the permeability to its cell content and death happens [26]. Garlic oil alkalinizes fungal cell contents, disrupts fungus cell membrane by inhibiting lipid synthesis [27].
2. Ergosterol Biosynthesis Inhibition: Ergosterol is an essential part of fungal cell membrane. Disrupting cell membrane integrity is possible through the inhibition of biosynthesis of ergosterol when incident to essential oils [28].
3. Essential oils interfere with Cellular Metabolism: Interference with key metabolic pathways, like glycolysis, inhibits the fungal growth, survival.
4. Some essential oils generate ROS which disrupt fungal cellular components including DNA, proteins and lipids thereby causing cell death. It has been shown that allicin induces oxidative stress in fungal cells and eventually apoptosis and growth inhibition [9].
5. Upon Garlic oil exposure the fungal thiol-containing enzymes, which are essential for fungal metabolism and survival, are inhibited [29].

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IV. FORMULATION OF EMULGELS FOR NAIL INFECTIONS

The formulation of emulgels mainly involves the steps of selection of emulsifiers and stabilizers to ensure preparation of stable nano emulsion followed by thorough mixing to achieve a uniform dispersion that can be effectively integrated into the gel matrix.

a. Preparation of Nanoemulsions: Natural oils as well as the surfactants and co surfactants are used in the preparation of nano emulsions. Also, the titration method is often used to manufacture stable nanoemulsions with small droplet size for drug delivery and increasing permeability [30, 31].

b. Incorporation in to gel matrix: The availability of the nanoemulsion with a sustained release capability is achieved by adding the nanoemulsion to a gel base composed of a gelling agent, most commonly HPMC or Carbopol. The gel matrix is used to sustain the release of constitutional active ingredients and also to maintain the stability of the formulation [32].

c. Addition of Permeation enhancers: Thioglycolic acid, often is added to enhance permeation delivery to the transungual drug [31]. The barrier properties of the skin are altered at these enhancers and they facilitate deeper penetration and enhanced therapeutic agent bioavailability within the formulation. This innovative approach not just enhances efficacy of the treatment but also decreases likelihood of potential side effects, making also patient friendly experience is possible. Nail structure encasing as thick and keratinized allows the penetration of garlic oil to be restricted [33], hence, the need for enhancers and/or alternative delivery systems.

V. ADVANTAGES OF EMULGELS IN NAIL INFECTION TREATMENT

1. It has sustained Drug Release: The gel matrix in emulgels helps control release of the active agents, thereby prolonging the duration of the active property [31, 32].

2. Small Droplet Size and use of Permeation enhancers: The nano emulsions have a small droplet size and the use of permeation enhancers allow penetration of the active ingredients in the nail plate not possible with other formulations [31, 32].

3. Lower Degradation: Emulgels are prone to degradation compared to traditional emulsions, and therefore maintain consistent therapeutic efficacy [31]. The unique structural characteristics of emulgels are the reasons for their effectiveness as a delivery system. Because emulsions are thermodynamically unstable systems, the stabilizing effect of the gel matrix avoids phase separation and produces a homogenous distribution of the natural oil within the formulation [44].

4. Emulgels are of easy application, they have good spreading action, and are less greasy relative to the traditional ointments of which patients are more compliant [34].

VI. EFFICACY OF EMULGELS IN TREATING NAIL INFECTIONS

Many studies have shown the efficacy of emulgels in treating nail infections.

1. **Antifungal activity:** The antifungal activity of emulgels in loads comprising natural oils has been very high against pathogens Trichophytonrubrum and Candida albicans. For instance, the nanoemulgel containing Timur oil and rosemary oil formed a higher zone of inhibition than marketed ketoconazole cream [30]. Specifically, one polyherbalemulgel composed of ginger, turmeric, clove oil and neem was developed by us and a polyherbalemulgel was evaluated on various antifungal activity. Breath mint flavor was utilized, as well as clove oil to improve permeation. Emulgel has antifungal activity potential. It is reported that herbal combination optimizes medication delivery effectiveness [35]. Natural oil can enhance the antifungal efficacy of emulgel systems through stronger antifungal activity of micro emulgel against Candida albicans in comparison with other formulation [36].
2. **Emulgels for transungual delivery:**Emulgels have been shown to be capable of transungual delivery of antifungal agents at levels expected to be therapeutically effective. For example, ketoconazole nanoemulgel exhibited 77.54% transungual permeation in 24 hours and is higher than drug suspension [31]. This suggests that emulgels could be a potential alternative, not only because it has improved drug delivery but also improved antifungal potency, in enhancing treatment efficacy of nail infections. The results from the study show that the eugenol linalool emulgel had shown antifungal activity for Trichophytonrubrum with complete recover in rabbits and suggest its effectiveness in other formulation and conditions for the treatment of fungal infections [37]. According to a 2018 study published in Journal of Medicinal

Mycology, it was concluded that garlic oil had significant inhibitory activities against fungal biofilms, which have been demonstrated to play a role in the persistence of onychomycosis. In 2020, a clinical study was conducted by research team showing that garlic oil applied topically could improve nail appearance and reduce the fungal load in patients with mild to moderate onychomycosis [33].

3. **Safety and Tolerability:** Safety and non-irritancy of emulgels in skin irritation have been demonstrated and they are considered suitable for topical application [31, 32]. Antifungal activity of emulgels containing Melaleucaalternifolia and Cymbopogonflexuosus essential oils was evaluated against Candida albicans and it was found to have a great potential for management of for vulvovaginal candidiasis [39]. Emulgel containing TOH showed an antifungal activity to 30 species of human pathogenic fungi with no skin irritation and cosmeceutical benefits also [40]. Garlic oil has proven to have a good established safety profile with minimal side effects when compared to oral antifungals [27].

VII. FUTURE PERSPECTIVES AND CHALLENGES

Certain challenges need to be addressed in order for emulgels to be used for treating nail infections, as these products have promise.

1. Complexity of Formulation Process: The large scale production of emulgels might be difficult as the formulation process is complicated. Cost effective methods of industrial scale production are needed [3, 34].

2. But there are Stability issues which come due to Natural oils overtime. Garlic oil contains allicin which is unstable and dissolves quickly, losing the potency of it over time [38].

3. Emulgels are likely to be facing regulatory hurdles as they are a relatively new drug delivery system. Safety and efficacy of them need further studies and clinical trials to establish their safety and efficacy for regulatory approval [3, 41].

4. Patient education about the correct use and application emulgels is essential to obtain proper effect and safety [34, 41].

VIII. CONCLUSION

Natural oils are being delivered in the treatment of nail infections using emulgels as a promising carrier system. They are attractive in that they are able to offer sustained release, improve stability, and increased permeability, as compared to conventional formulation. Work still needs to be done to make their potential fully realized and to put them into use on a large scale in markets. This study provides a comprehensive exploration of the use of emulgels as a carrier for the natural oils and their formulation advantages, efficacy and safety as carriers for the natural oils to be used for the treatment of nail infections.

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